REMARKS

Claims 1-5, 9-13, 16-35, 39-43 and 46-51 were rejected under 35 U.S.C.§112, second paragraph, for failing to particularly point out and distinctly claim the subject matter that the applicant regards as the invention.

Reconsideration is requested.

The term "high solubility" was objected to in that it was unlear if the active agents have a high solubility in water or a different medium. In response, claim 1 has been amended to recite that the "high solubility active ingredient has a solubility where less than 1 part to 30 parts of water is required to dissolve 1 part of active ingredient".

The Examiner objected to the use of the term "as described in the USP". The claims have been reviewed and all detected references to the term "as described in the USP" have been cancelled. The use of the term "USP" is considered proper because the "USP" is a recognized compendium of standards to identify a particular material and that does not raise a question of indefiniteness. While it is true that the "USP" may change its standards, this does not mean that it is improper in a patent claim to refer to that standard because the original standard, if changed, will still be ascertainable.

Claims 1-5, 9-13, 16-35, 39-43 and 46-51 would be understood by one skilled in the art to reflect weignt ratios and for this reason the claims have been amended to specify that the ratios are weight ratios.

Claim 21 has been canceled and the use of the term "potent" is now moot.

In response to the objection to the use of a "range within a range", claim 25 has been revised to only specify twice a day administration and new claim 61 now specifies "once a day" administration. Claim 28 has been amended to delete the trademark Eudragit RS as the generic terms that describe this producat were also used in the original claim. For these reasons, it is requested that this ground of rejection be withdrawn.

Claims 1-5, 9-13, 16-23, 25-26, 30-35, 39-43 and 46-60 were rejected under 35 U.S.C. §103(a) as being unpatentable over Timmins et al. (Timmins).

Reconsideration is requested.

Claim 1 has been amended to point out the preferred hyrophobic release control agents that are in the matrix and the preferred hydrophobic release controlling agents that form the coating. Support for this amendment is found in original claim 3 and in the specification at page 3, para 45-47.

Many modified delivery systems utilize a matrix dosage form that provides for useful levels of controlled release in the delivery of sparingly soluble drugs. For soluble drugs, however, and particularly for highly soluble drugs, such matrix formulations do not provide adequate control over the release rate, instead resulting in a drug release profile that approximates first-order kinetics along with dose dumping or a burst release that makes the matrix formulation unacceptable for use with soluble drugs. However, since many modified release dosage forms contain comparatively large amounts of highly soluble active ingredient it is often necessary to include large amounts of suitable excipients to achieve appropriate controlled release profiles. This results in an over sized dosage form which causes patient rejection due to the difficulty in swallowing the over sized dosage form. Hence a technique is

needed, which can effectively control the release of the highly soluble active ingredient without requiring an over sized dosage form. The amended claims point out that a matrix is made of active ingredient and a particular hyrophobic agent. The matrix is then coated with a hydrophobic agent.

The Timmins patent was cited in the present specification at page 1, paragraph 006 where the applicants distinguished Timmins from the claimed invention as follows:

> A biphasic controlled release delivery system for metformin hydrochloride, which has prolonged gastric residence and that swells following hydration. The ratio of inner solid phase to outer continuous phase is 0.5:1 to about 4:1. The major limitation of this invention (i.e. Timmins) is that it provides a very bulky formulation for higher doses of the metformin hydrochloride that is very inconvenient for human consumption. For instance, example cited provides formulation of 500mg metformin with tablet weight of 1.0gm. Hence restricting to the low dose sustained release tablets of 500mg and slightly more and making it obligatory to take two tablets of 500mg each time to provide sustain[ed] action. The cited example teaches use of combination of at least one hydrophilic polymer and which is essential part for swelling. Non-swellable or non-erodable formulations are not included in the invention.

It is clear from the brief description as well as specification that Timmins operates by increasing the time that the dosage remains in the stomach as a result of the swelling of the formulation. This essential functional characteristic is only achieved by the use of polymers that swell on contact with

water. Therefore, although Timmins has mentioned an inner solid particulate phase and outer solid continuous phase that use one or more hydrophilic polymers, one or more hydrophobic polymer and/or one or more hydrophobic materials, the Timmins composition requires at least one hydrophilic polymer, as shown by reference to all of the enabling examples of that patent. Hence, in the implementation of the teachings of Timmins, a skilled person would be directed to use at least one hydrophilic polymer if that person was following the teachings of Timmins in making a sustained release formulation. This does not make obvious the use of the dual retard techniques, as recited in claim 1 and the other claims of the present application because that technique incorporates **only hydrophobic polymers.**

It is not disputed that matrix formulations of highly soluble drugs will require high amounts of polymers to achieve a controlled release profile. This results in an increase in the size of the dosage form. This problem has been mentioned by Timmins but Timmins does not suggest the dual retard technique as pointed out in the claims of the present application and does not teach the claimed solution to the problem of increased dosage sizes.

In Timmins, the final size of the dosage form becomes very large due to large quantity of polymer required and thus the Timmins approach to formulations of drugs that must be administered in high doses, such as metformin, is not practical due the difficulty in swallowing that is very common in older patient populations. The following Table is derived from Timmins and it illustartes the high amounts of polymer relative to the active pharmaceutical ingredient (API) that result from the Timmins technique.

Example-1	500g API + 376.5g polymer	75% polymers by wt of API
Example-2	500g API + 391g polymer	78% polymers by wt of API
Example-3	500g API + 408 g polymer	81% polymers by wt of API
Example-4	500g API + >400 g polymer	81% polymers by wt of API

If we compare examples for the same drug as shown in the the present specification (e.g. Example 8 = 20% polymer), the final size of the dosage form will actually be much smaller as compared to the Timmins dosage form. Thus, it is clear from above that the problem, though mentioned in Timmins, is actually not solved by invention whereas it is actually solved in instant invention.

While the disclosed range of polymer in Timmins seems overlapping to the claimed ratio of instant invention, Timmins does not teach the sustained release formulation of high solubility drugs using a reduced quantity of polymers by using the dual retard technique.

In the present specification at page 5, paragraph 0063, it was disclosed that: "FIGS. 2 and 3 show release of high solubility active agent 5 & 6 and 9 & 10 as per example 1 & 2 respectively from a dosage form prepared using dual retard technique and release of high solubility active agent 7 & 8 and 11 & 12 as per example 3 & 4 respectively from a dosage form prepared without using dual retard release technique. (Thus fig-2 discloses plots of dissolution of dosage form prepared using dual

retard technique & fig-3 discloses plots of dissolution of dosage form prepared without using dual retard technique) The total quantity of the hydrophobic release controlling agent is same in all the dosage forms. The figures clearly show that the use of dual retard technology significantly reduces the burst effect and effectively controls the release rate of the high solubility active ingredient for prolonged period. FIG. 4 shows release of high solubility active agent 13 & 14 as per example 8 from a dosage form prepared using dual retard technique and release of high solubility active agent 15 & 16 as per example 11 from a dosage form prepared without using dual retard release technique. The total quantity of the hydrophobic release controlling agent is same in all the dosage forms. In spite of that the figures clearly show that dual retard technology significantly reduces the burst effect and effectively controls the release rate of the high solubility antidiabetic active ingredient for prolonged period."

The quoted section of the specification indicates that to achieve a desired release profile without burst effect, a reduced amount of polymers are required if the dual retard technique, recited in the claims of the present application, is implemented.

This discovery is also confirmed by all of the examples of Timmins, who used very high amounts of polymers to achieve a useful controlled release profile for highly soluble drugs. This is achieved by the dual retard technique even though

substantially reduced quantities of polymers are used which have the positive and practical improved result of providing controlled release formulations in a compact dosage form even for high dose drugs.

The formulation of highly soluble drugs in a compact form results from the formulation recited in claim 1 and the other claims of the present application. An additional example of a particular drug that is amenable to formulations according to the claimed invention is sustained release Levetiracetam which is approved by the Food and Drug Administration as a 500mg tablet for once daily administration. However the approved dosage and administration starts with 1000mg daily and hence two tablets (sustained release) of 500mg must be taken by the patient which is inconvenient to the patients. This appears to be a direct result of the large size that would result if prior art technology was used to formulate a 1000mg. controlled release tablet. In case of instant invention due to the very low quantity of polymer required, the same high dose-high solubility drug, Levetiracetam can be prepared with acceptable size even with 1000mg strength, for administration as a **single dosage form**. This clearly shows the advantages of the reduction in the size of conrtrolled release dosage forms according to the present invention as defined by the claims.

Timmins teaches a drug delivery system which achieves extended gastric residence by virtue of size but does degrade *in vivo* so as not to cause obstruction of the gastrointestinal tract. Thus, Timmins is limited to gastroretentive dosage forms and teaches away from any other type of dosage form that does not swell in the stomach in order to retard its passage in the gastrointestinal tract.

For these reasons, it is requested that this ground of rejection be withdrawn.

Claims 24, 27-28 and 29 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Timmins and Merck Index.

Reconsideration is requested.

Timmins has been distinguished from the claimed invention above as only teaching the concept of formulating a dosage form so that it swells sufficiently to be gastroretentive. The claimed dosage forms of valproic acid and niacin are not formulated to be gastroretentive and they do not have an absorption window. Thus, the teachings of Timmins can not be applied to these drugs. For these reasons, and the comments set forth above with regard to Timmins, it is respectfully submitted that claims 23, and 25 are not obvious under 35 U.S.C. 103(a) over Timmins and Merck Index.

An early and favorable action is earnestly solicited.

Respectfully submitted,

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